

# The Challenge of Disentangling Parkinson's-related Fatigue and Neuropsychiatric Symptoms

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## Abstract

Fatigue is among the most prevalent and debilitating non-motor symptoms in Parkinson's disease (PD). In the focal article, "Screening cut-off scores for clinically significant fatigue in early Parkinson's disease", we discussed the challenges of evaluating fatigue in PD and proposed cut-off scores for select fatigue assessments. This commentary expands on the challenges of evaluating fatigue, especially when it presents alongside psychiatric symptoms. We examine and compare the similarities of fatigue and depression, anxiety, and apathy. Overlapping symptoms include reduced motivation, difficulty sustaining attention, and diminished energy. The challenge of disentangling the phenomena is further complicated by symptoms of PD, which may present with similarities to psychiatric symptoms (e.g., bradykinesia, masked facies, and sleep disturbances). Accurate evaluation and diagnosis of each condition is necessary for a comprehensive approach to PD patient treatment and symptom monitoring.

**Keywords:** Parkinson's disease, Fatigue, Avolition, Non-motor symptoms, Depression, Anxiety, Apathy

## Introduction

In the article, "Screening cut-off scores for clinically significant fatigue in early Parkinson's disease", cut-off scores were established for improved use of two subjective fatigue assessments [1]. Within the article, the challenges of evaluating clinically significant fatigue in Parkinson's disease (PD) were discussed. This commentary builds on the challenges of assessing non-motor symptoms in PD, as the symptoms of fatigue may intersect with and further complicate evaluation of other psychiatric symptoms also common in PD.

## Fatigue in Parkinson's Disease

Recent surveys reported 58-68.5% of Parkinson's patients complained of fatigue symptoms [2,3]. Among the most common of the non-motor symptoms in PD, fatigue is multidimensional, existing in dissociable mental and physical

domains and as subjective fatigue and objective fatigability [4-6]. The dimensions consist of categories of symptoms that do not have to coexist. Adding to the complexity of the symptoms of fatigue in PD, they differ from that of fatigue in other clinical groups and the general population [4]. In proposed diagnostic criteria for PD-related fatigue, patients must report attenuated energy levels and the perception that more effort must be exerted relative to the activity being performed. Additional criteria include non-restorative rest and fatigue symptoms that may be worsened by cognitive tasks requiring sustained attention [5]. Moreover, the complexity of symptoms can increase the potential of PD patients presenting with symptoms that are similar to those in psychiatric disorders. However, as noted in the focal article of this commentary [1], the challenge of evaluating fatigue in PD is that there is no single definition or assessment to diagnose patients with clinically significant PD-related fatigue. Unlike psychiatric disorders which follow strict adherence to diagnostic criteria

in the *Diagnostic and Statistical Manual for Mental Disorders* (DSM) or *International Classification of Diseases* (ICD), the recently proposed diagnostic criteria for PD-related fatigue [5] are not currently being used in all research and clinical environments.

### Fatigue and Depression

A meta-analysis identified a significant association between fatigue and depression in eighty percent of the studies reviewed [7]. However, the reports of depression in PD varies significantly from 2.7-90%, likely arising from differences in whether the researchers used *DSM* diagnostic criteria or that of a self-report survey [8]. Although fatigue and depression are independent phenomena, PD patients experiencing significant fatigue are at greater risk of exhibiting symptoms of depression. In clinical application, diagnosis of depression would follow the guidance of the *DSM*. *DSM-5-TR* diagnostic criteria for major depressive episode include "fatigue or loss of energy" and "diminished ability to think or concentrate" [9]. Although additional symptoms must be present to meet criteria, this indicates that an individual experiencing significant fatigue in PD could partially meet criteria for depression. When fatigue symptoms are combined with symptoms of PD, such as bradykinesia and sleep disturbances, patients are more likely to meet diagnostic criteria for major depressive disorder. Moreover, if the PD patient is taking a self-report depression scale, the symptoms of PD and fatigue may further complicate interpretation of the score. For example, the Patient Health Questionnaire (PHQ-9) contains the following symptoms (not inclusive) for self-evaluation: trouble falling or staying asleep, feeling tired or having little energy, trouble concentrating on things, and moving or speaking so slowly that other people could have noticed [10]. The challenge of accurately diagnosing depression in PD is further complicated with the presence of comorbid syndromes such as fatigue and other psychiatric symptoms.

### Fatigue and Anxiety

Like depression, the prevalence of anxiety disorders in PD is also reported as a wide range from 3.6-40% [11]. The most common anxiety disorders in the PD population include panic disorder, generalized anxiety disorder (GAD), and social phobia. Anxiety disorders also have a unique manifestation in PD and are often influenced by other PD symptoms. For example, panic attacks are associated with incidents of freezing of gait and off-periods. Symptoms of panic attacks may be further exacerbated if the patient is also suffering from dysautonomia [12]. Of the anxiety disorders, GAD presents most similarly to fatigue in PD. Some symptoms included in the diagnostic criteria for GAD include, "being easily fatigued" and "difficulty concentrating and mind going blank" [9]. Like depression, additional diagnostic criteria are also symptoms of PD such as "muscle tension" (i.e., rigidity) and "sleep disturbance". Sleep

disturbances, in particular, can be difficult to disentangle. A valid question to consider is whether a patient's fatigue symptoms are a result of impaired sleep. If so, was the sleep disturbance caused by uncontrolled anxiety symptoms or a PD-related sleep disorder? In a clinical setting, diagnosis of an anxiety disorder would follow diagnostic criteria. However, as previously noted, in many research contexts, self-report surveys are used to evaluate severity of anxiety symptoms. Although anxiety is more easily dissociable from fatigue, its role as a strong predictor of fatigue cannot be ignored [13].

### Fatigue and Apathy

Apathy is recognized as a lack of emotion, emotion expression, interest, and motivation. The syndrome is common in PD and mental health disorders such as major depressive disorder, neurocognitive disorder, and as avolition in schizophrenia [9]. Like fatigue, apathy is also argued to exist in multiple domains: affective, cognitive, and behavioral [14]. Apathy also shares symptoms with PD, such as blunted emotional expression (i.e., masked facies) and lack of spontaneous action (i.e., bradykinesia). Compared to depression and anxiety, apathy poses a great challenge due to the subjective nature of both fatigue symptoms and apathy. Like fatigue, apathy has a recently proposed set of diagnostic criteria for brain [15] and neurocognitive disorders [16], but it is not uniformly used in the treatment or evaluation of apathy. Rather, self-report surveys remain the common method for assessing apathy symptom severity. However, unlike depression and anxiety, apathy and fatigue do not have clearly defined treatments available. Medications such as rivastigmine, intended to treat mild cognitive impairment, have been found to be effective in alleviating symptoms of apathy [14]. Similarly, methylphenidate, a psychostimulant, is used to treat fatigue [17]. The starkly different paths for treatment of apathy versus fatigue also emphasizes the importance of disentangling the two phenomena.

### Conclusion

In a recent study, ninety-nine percent of PD patients reported the presence of at least one non-motor symptom [3]. The impact of non-motor symptoms is debilitating and severely impacts patient quality of life. Comprehensive evaluation of PD patients not only requires recognition of non-motor symptoms but also careful differentiation between phenomena with similar clinical presentations. While clinicians may have increased awareness and education on neuropsychiatric disorders such as depression and anxiety, they should not overlook the potential presence of fatigue symptoms. As noted in the focal article of this commentary [1], improved methods for evaluating subjective fatigue in PD will be essential for a comprehensive approach to PD patient treatment and symptom monitoring.

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## Author Contributions

AXAH drafted the manuscript. AXAH and JSL edited and approved final manuscript for publication.

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